



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP - 7 2000

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Mark P. McGrath, Esq.
395 School Street
Watertown, MA 02472

Re: Docket No. 99P-4053/CP1

Dear Mr. McGrath:

This letter responds to the citizen petition dated August 31, 1999, submitted on behalf of Drs. Timothy Maher and Richard Wurtman, and supplemented on December 16, 1999, and March 4, 2000. Additional comments regarding your petition, which we considered in formulating our response, were provided on behalf of Medeva Pharmaceuticals by Dr. Terence Coyne on November 4, 1999, and David M. Cohen on November 15, 1999, and May 4, 2000. In addition, a previous scientific presentation of these data by Dr. Wurtman to some of the Agency's review personnel was also considered.¹

Your petition pertains to the current labeling for phentermine and requests that the product labeling and patient insert for phentermine in all of its salt forms indicate that it inhibits the enzyme monoamine oxidase, classifying it as a monoamine oxidase inhibitor. You request that the current language of the approved labeling and patient insert be modified to state that phentermine is capable of inhibiting monoamine oxidase (MAO) and should not be used concurrently with sympathomimetic amines or selective serotonin reuptake inhibitors (SSRIs). For the reasons discussed below, your citizen petition is denied.

I. BACKGROUND

A. Phentermine Labeling

Phentermine is a sympathomimetic amine approved for use as an anorexigenic agent. It is available from several pharmaceutical manufacturers and comes in two forms, phentermine hydrochloride and phentermine resin. The pertinent sections of the labeling for this class of drugs include the following:

Description: Phentermine is a sympathomimetic amine with pharmacologic activity similar to the prototype drugs of this class used in obesity, the amphetamines. Actions

¹Dr. Wurtman presented the scientific data to some members of the Division of Metabolic and Endocrine Drug Products, and the Division of Neuropharmacologic Drug Products, February 3, 1999.

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include central nervous system stimulation and elevation of blood pressure . . .

Drugs of this class used in obesity are commonly known as "anorectics" or "anorexigenics." It has not been established however, that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions, or metabolic effects, may be involved, for example.

Indications: *Phentermine is indicated as a short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥ 30 kg/m², or ≥ 27 kg/m² in the presence of other risk factors (e.g., hypertension, diabetes, hyperlipidemia).*

Warnings: *Phentermine is indicated only as short-term monotherapy for the management of exogenous obesity. The safety and efficacy of combination therapy with phentermine and any other drug products for weight loss, including selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline, fluvoxamine, paroxetine), have not been established. Therefore, the coadministration of these drug products for weight loss is not recommended.*

Contraindications: *Advanced arteriosclerosis, cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma.*

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

Precautions: *Caution is to be exercised in prescribing phentermine for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of phentermine and the concomitant dietary regimen.*

Phentermine may decrease the hypotensive effect of adrenergic neuron blocking drugs.

B. Monoamine Oxidase

Monoamine oxidase (MAO) is an enzyme that metabolizes the neurotransmitters, dopamine (DA), serotonin (5HT or 5-hydroxytryptamine) and norepinephrine (NE). The two forms of MAO — MAO-A and MAO-B — differ in body tissue distribution, sensitivity to different inhibitors, and substrate specificity. The distribution of the two forms varies among species.

MAO plays an important role in modulating the physiologic levels of neurotransmitters. Inhibition of the MAO enzyme results in increased neurotransmitter concentration and activity. Depending on their degree of binding to the enzyme, monoamine oxidase inhibitors (MAOIs) are classified as either reversible or irreversible.

An acute increase in the synaptic levels of any of the neurotransmitters or a change in the level of the enzyme modulators can lead to the occurrence of acute adverse side effects. Hypertensive crisis is the most serious adverse reaction associated with MAO inhibition. Another risk is the abnormal increase of serotonin that may occur if an MAOI is coadministered with a selective serotonin reuptake inhibitor (SSRI) drug. The resulting reaction manifests as "*serotonin syndrome*" — fever, muscular rigidity, nausea, and alterations in level of consciousness. Both hypertensive crisis and serotonin syndrome can be life threatening.

II. DISCUSSION

You provided a collection of information to support your assertion that phentermine is an MAOI and that the currently approved product labeling should be changed to reflect this property of phentermine. Your request is based on data from several published studies and an unpublished (unrevised) manuscript.²

A. Is Phentermine a Monoamine Oxidase Inhibitor (MAOI)?

Drs. Maher and Wurtman provided data to demonstrate that phentermine inhibits MAO *in vitro*. IC_{50} (molar inhibitory concentration that inhibits the enzyme activity to 50%) values reported for MAOI activity ranged from 180 μ M to 40 mM in studies by Nielsen and Dubnick (1970) and Seiler and Wassermann (1973). In an unpublished study, Ulus, I.H., et al., reported K_i 's (degree of MAO inhibition) for phentermine's inhibition of MAO-A and MAO-B of 76-89 and 310-416 μ M, respectively (Unrevised manuscript, 1999). However, phentermine's MAOI activity was observed at inhibitory concentrations higher than those of other compounds, even those characterized as "relatively weak" MAO inhibitors (e.g., chlorphentermine). Ulus et al., directly compared MAOI activity of phentermine with that of recognized irreversible and reversible MAOIs. Unfortunately, MAOI activity was not expressed in the same units for phentermine (K_i) and the other compounds (EC_{50}), so a direct comparison was not possible. It is noted that in this *in vitro* environment, phentermine exhibited MAOI activity, but at concentrations markedly higher than those for irreversible MAOIs (e.g., clorgyline, tranylcypromine).

In a letter to *Synapse*, Dr. Richard Rothman raised the point that phentermine's IC_{50} values for MAOI activity are far above the plasma levels of phentermine achieved *in vivo* at therapeutic

²The revised manuscript (not provided for review) was recently accepted for publication in the *Journal of Biochemical Pharmacology*.

doses.³ He stated that plasma phentermine levels of approximately 0.7 μM are achieved following daily oral phentermine doses of 37 mg/day. Medeva Pharmaceuticals provided a table summarizing plasma data from some clinical trials. Peak plasma levels of phentermine ranged from approximately 0.5 to 1.0 μM following the highest dose for which data were available (30 mg/day). These levels are far below the reported IC_{50} and K_i values reported for phentermine's *in vitro* MAOI activity. It is difficult, however, to directly compare *in vitro* inhibitory concentrations with *in vivo* plasma data due to a variety of factors, e.g., oral bioavailability, tissue distribution/accumulation, and formation of active metabolites. In a study by Morita and Mehendale, phentermine did not exhibit greater MAOI activity when administered *in vivo*.⁴

In vivo, MAOI activity has been assessed by measuring the effects of various compounds on plasma 5HT and its metabolite, 5-HIAA. MAOIs have been reported to increase plasma levels of 5HT and decrease those of 5-HIAA.⁵ Phentermine, when administered to healthy male volunteers at a single dose of 15 mg, had no significant effect on plasma 5HT levels.

From these studies, it would appear that phentermine inhibits MAO *in vitro* if the concentration of the drug is high. Conversely, the evidence presented for phentermine does not support MAO inhibition *in vivo* under usual clinical conditions and at anticipated therapeutic levels.

B. Should the Labeling Be Changed?

You request that phentermine labeling be modified as follows:

Phentermine is capable of inhibiting monoamine oxidase (MAO) and therefore should not be used concurrently with sympathomimetic amines or selective serotonin reuptake inhibitors (SSRIs).

Current labeling includes a warning against the coadministration of phentermine and other drug products for weight loss, including SSRIs, and a contraindication of use of the drug during or within 14 days following administration of monoamine oxidase inhibitors because of the potential for hypertensive crises.

In response to a previous request from Drs. Maher and Wurtman, the FDA addressed the issue of the potential MAOI activity of phentermine. The Division of Metabolic and Endocrine Drugs and the Division of Neuropharmacologic Drug Products reviewed material submitted by Drs.

³"Is Phentermine an Inhibitor of Monoamine Oxidase? A Critical Appraisal," *Synapse*, Vol. 32: 141-145, 1999.

⁴"Effects of Chlorphentermine and Phentermine on the Pulmonary Disposition of 5-Hydroxytryptamine in the Rat *in vivo*," *American Review of Respiratory Disease*, 127:747-750, 1983.

⁵Celada et al., *Journal of Neural Transmission*, Vol. 32:149-154 (Suppl), 1990.

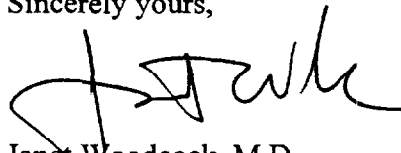
Maher and Wurtman. In addition, the Division of Drug Risk Assessment conducted analyses on the Adverse Experience Reporting System/Spontaneous Reporting System (AERS/SRS) databases to assess the MAOI activity of phentermine. At that time, it was concluded that there was no evidence that phentermine is a clinically relevant MAOI.

Since then, the only new relevant data are those generated by Ulus et al. (1999). As noted above, phentermine appears to inhibit MAO *in vitro* if the concentration of the drug is high. The evidence does not support a finding that phentermine inhibits MAO *in vivo* under usual clinical conditions and at anticipated therapeutic levels. In our view, therefore, current labeling is adequate to communicate the risk of concomitant administration of phentermine with drug products of other pharmacologic categories.

III. CONCLUSION

Although you provide data demonstrating that phentermine is capable of inhibiting monoamine oxidase, neither these data nor FDA's analysis of the AERS/SRS databases support the position that phentermine is a clinically relevant MAOI. Current product labeling for phentermine (all forms) states in the WARNINGS section that co-administration of phentermine with other weight-loss drug products (e.g., SSRIs) is not recommended since the safety and efficacy of such combinations have not been established. There is very little evidence to suggest that phentermine is an MAOI or that it alters 5HT metabolism by some other mechanism in a clinically meaningful way. The data submitted in support of your petition do not support the conclusion that phentermine is a clinically relevant MAO inhibitor or that the current labeling for phentermine is insufficient for safe use of the drug. Accordingly, your petition is denied.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'J. Woodcock', is written over the typed name.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research